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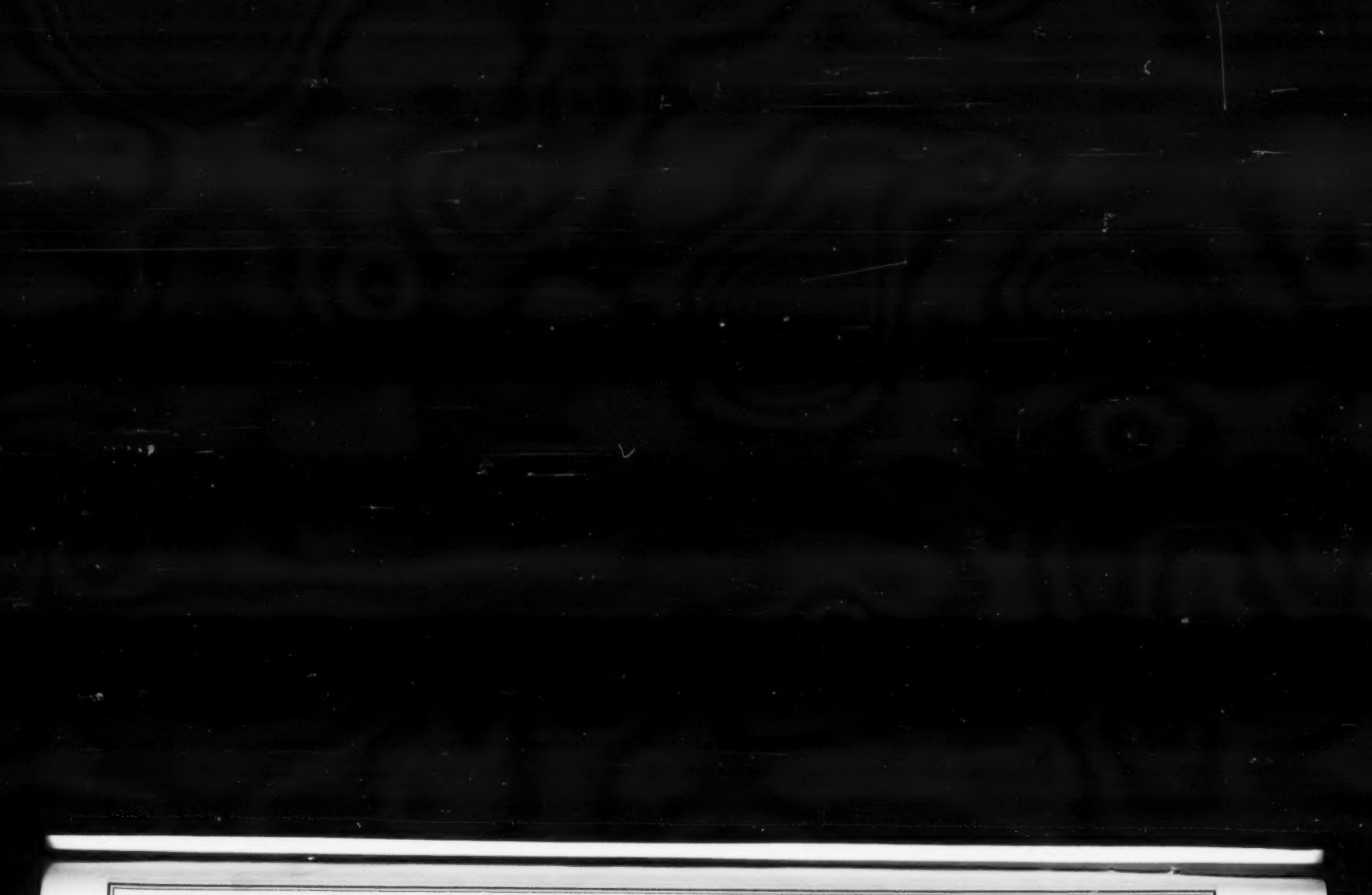

Read McLane Ellsworth

August 29, 1899-April 28, 1936

The Editorial Board of the BULLETIN OF THE JOHNS HOPKINS HOSPITAL records with deep regret the death of Dr. Read McLane Ellsworth on April 28, 1936. Appointed Managing Editor in March, 1935, he carried out the duties of that position with energy and enthusiasm.

Dr. Ellsworth was graduated from Reed College, Portland, Oregon in 1920 and from the Johns Hopkins University School of Medicine in 1924. After serving as House Officer at the Massachusetts General Hospital, he joined the Resident Staff of the Johns Hopkins Hospital. His career was interrupted by illness when he was Resident Physician, but he returned to his duties the following year as a member of the Department of Medicine and was an active teacher and investigator until his last illness. His scientific contributions, the majority of them completed during the last five years of his life, include important studies upon the functions of the parathyroid glands, the adrenals and the hypophysis.

To his students and his colleagues he brought a contagious enthusiasm balanced by a discriminating critical faculty. In addition to his scientific interest in Medicine he cultivated a deep appreciation of literature and music. Widely read and a brilliant conversationalist, he shed his buoyant eagerness upon all who came to know him.

His many friends will recall with admiration his steadfast refusal to bow before his illness and his persistent optimism in the face of the limits set thereby. They will remember, with a profound sense of loss, his energetic, charming personality.

INTRANUCLEAR INCLUSION BODIES IN THE KIDNEY AND LIVER CAUSED BY LEAD POISONING

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Submitted for publication May 4, 1936

The intranuclear inclusion bodies which are described in this paper were found in tubular epithelium of the kidneys and in liver-cells of twenty-one children dying from the effects of relatively acute lead poisoning and lead encephalitis. While it is well known that lead is capable of producing changes in the epithelial cells of the kidney which are somewhat similar to the lesions caused by other heavy metals (1), the effect of lead poisoning on the function of the kidney is not very familiar. No clinical evidence was found in any of these children, however, which would indicate appreciable impairment of the function of the kidney, and we are not concerned here with the problematical relationship between plumbism and chronic nephritis. The cases to be described are of interest because the acidophilic inclusion bodies in liver and kidney and other changes in the basophilic chromatin of the nuclei resemble in many respects the nuclear lesions found in association with some virus diseases.

The nature and significance of inclusion bodies have been subjects of the keenest interest ever since the earliest descriptions of certain peculiar intranuclear inclusions by Jesionek and Kiolemenoglou (2) and by Ribbert (3) in 1904. The historical review of Von Glahn and Pappenheimer (4) in 1925, and that of Farber and Wolbach (5) in 1932, show how opinion concerning inclusion bodies has been modified from time to time. It is familiar knowledge that intranuclear inclusions were usually described as "protozoan-like cells" and were thought to be parasites until the work of Goodpasture and Talbot (6) and of Lipschütz (7) in 1921. Goodpasture and Talbot concluded that the bodies were not protozoa and compared them with the nuclear changes in the cutaneous lesions of chickenpox which Tyzzer (8) had described in 1906. Lipschütz reported the production of intra-

nuclear inclusions in the tissues of man and rabbits infected with the virus of herpes, and he looked on the inclusions as representing specific reactions to a living virus, while Müller (32) supposed the "protozoan-like cells" to be damaged tissue cells in which dissociation of acidophilic and basophilic chromatin of the nuclei took place. At about the same time Levaditi (9) (10), Luger and Lauda (11), Lauda (12), de Fano (13), Zdansky (14), and Cowdry and Nicholson (15) took the view that intranuclear inclusion bodies represented non-specific abnormalities in damaged cells, and it was pointed out that they possessed staining properties like some of the normal intranuclear materials.[1]

The idea that inclusions were specifically related to virus infection gained in favor, however (17), and the view was sometimes expressed that the presence of inclusion bodies was pathognomonic of a virus infection. It has lately become apparent that inclusion bodies are in fact variable in morphology, staining properties, and in mode of production, and this has been suggested by Cowdry's classification of intranuclear inclusions into two types, A and B (18). The inclusions classified together as type A bodies occur in herpes, yellow fever, chickenpox, et cetera, and in the salivary glands of children, guinea-pigs, moles and in other animals without proven virus infection. They are described as being amorphous or particulate, but may be condensed to form solid masses, and there is evidence both for and against the idea that in some cases the granular forms, or elementary bodies, represent the living virus itself. The inclusions of this type are generally said to be acidophilic in reaction to dyes like eosin, fuchsin, and phloxin, and they contain little or no thymonucleic acid or masked iron. The nuclei in which type A inclusions develop are usually enlarged. The basophilic granules of chromatin tend to collect toward the nuclear membrane, leaving a clear zone more or less free of chromatin between the inclusion and the margins of the nucleus. The inclusion bodies classified in this group are actually diverse in

[1] Cowdry (16) has recently emphasized the fact that inclusion bodies resemble in certain respects the acidophilic material which is a constituent of many normal nuclei. Both intranuclear inclusions and certain materials in normal nuclei are acidophilic in staining properties, and contain little or no thymonucleic acid or masked iron, in contrast to the basophilic particles of chromatin in the nuclei.

many respects, however, and those found by Rector and Rector (19) in the salivary glands of moles are either basophilic, and give strongly positive reactions for masked iron and thymonucleic acid, or may consist of a central acidophilic core surrounded and obscured by a layer of basophilic chromatin granules. In morphology, too, the inclusions grouped together as type A bodies are variable. The intranuclear inclusions of yellow fever, for example, collect in the nuclei of liver cells to form several clumps, each composed of distinct discrete particles (20), in marked contrast to the circumscribed, homogeneous and plastic appearance of the intranuclear inclusions of chickenpox (8).

The inclusions of type B, as described by Cowdry (18), are found in poliomyelitis, epidemic encephalitis of horses (Borna's disease), Rift Valley fever, in some tumors, and in the tissues of many animals without evidence of disease. These are rounded, hyaline, acidophilic bodies of variable size, and they occur in nuclei which are otherwise not greatly altered. The basophilic chromatin is said not to be marginated, as in nuclei which contain inclusions of type A, and the nuclei seldom suffer complete necrosis (16). The larger inclusions of lead poisoning to be described here, as far as the bodies themselves are concerned, resemble the type B inclusions of Cowdry; but minute granular forms occur also, and the nuclei in which inclusions develop show alterations in size and shape and in the distribution of basophilic chromatin, which resemble the nuclear changes associated with inclusions of type A. Many cells and nuclei are destroyed completely.

It seems probable that the acidophilic intranuclear inclusions which appear in some diseases represent nothing more specific than abnormal nuclear material, and it is clear that they may be caused by factors other than infection with filterable viruses. This viewpoint has been advanced especially by the work of Cowdry (21), (22), (18), (16), and by the experimental production of a variety of nonspecific inclusion bodies. Heinbecker and O'Leary (23), by repeated electrical stimulation of axons, obtained changes in the nuclei of nerve cells which they briefly described as resembling the nuclear inclusions of virus diseases. Davenport, Ranson and Terwilliger (24) soaked nervous tissue in hypertonic salt solution and reported changes in some of the cells which were said to resemble intranuclear inclusion bodies. Watanabe (25) injected bacterial toxins into the cornea of rabbits, and changes

appeared in the nuclei which are said to resemble the inclusion bodies of herpes simplex. Recently Lee (26) injected various substances into cats, and the intravenous injection of salyrgan produced changes in nerve cells which are said by Cowdry (18) to be indistinguishable from type A intranuclear inclusion bodies. Pappenheimer and Maechling (27) found peculiar hyaline intranuclear and cytoplasmic inclusions in the tubular epithelium of the kidneys of two syphilitic patients treated with bismuth, and they reproduced similar inclusions in rats by means of bismuth. The inclusions caused by bismuth are very highly refractive, and differ especially in this respect from intranuclear inclusions found in other diseases and from the inclusions of lead poisoning.[2]

DESCRIPTION OF MATERIAL AND INCLUSION BODIES

Twenty-one cases of lead poisoning, all with symptoms of acute lead encephalitis, have been autopsied in this department in recent years. Clinical and anatomical evidence of lead poisoning is unmistakable in each case, and is summarized in table I. Most of the infants were poisoned by nibbling painted furniture. The blood content of lead was high in all of the cases in which the blood was examined (11 cases), and basophilic stippling of red blood cells was found in fourteen of the cases. In each case the lead line demonstrable in the bones by x-ray, as first described by Park (28) (29), is present in microscopical sections of ribs. In twelve of the cases the bones were examined by x-ray and the lead line was demonstrated. The brain was not examined in two cases, but the other nineteen brains show well developed microscopical lesions of lead encephalitis, lesions which are unlike those of epidemic encephalitis and the encephalitis which may appear after measles, pertussis, and vaccination against smallpox.

Acidophilic intranuclear inclusion bodies of identical appearance in each case are present in Henle's tubules and convoluted tubules of the kidneys, and in some of the liver cells in all of these examples of lead poisoning. In general, the inclusions in the kidney are found es-

[2] The nuclear inclusions reported by Pappenheimer and Maechling were neither acidophilic nor basophilic. In two cases which we have examined, however, some of the nuclear inclusions that form in the renal epithelium after injections of bismuth are readily stained by eosin and by phloxin.

pecially within nuclei which lie deep in the cortex, near the junction of cortex and pyramids, and they occur particularly in nuclei of cells which line tubules in the cortical rays. In some of the cases, however, they are also found in the labyrinthine parts of the cortex within nuclei of proximal convoluted tubules. The number of inclusions is variable in the different cases, but they are plentiful in each case. The distribution and size of the inclusions vary in any given portion of an affected tubule, and they are not scattered diffusely in all of the nuclei. Many are visible under the high dry objective in some of the cases, and the largest may be seen under the low power objective of the microscope.

When examined under the oil-immersion lens, the larger inclusions in the kidney are found to be sharply outlined, practically homogeneous, and are smooth in appearance. In stained sections they appear to have a refractive index slightly greater than that of the cytoplasm of the epithelial cells. Many of them are round, but some are irregular in shape, with indented margins. A good many are plastic in appearance, since they tend to assume the shape of hypertrophied and of other abnormal nuclei. The inclusions exhibit wide variations in size. There are many small bodies like droplets, a little larger than nucleoli, and many very small particulate ones may also be found. The largest inclusions observed in any case are somewhat larger than the nuclei of normal tubular epithelium, and the majority are intermediate in size between these extremes. The smaller inclusions may be found occupying any position in the nuclei, and basophilic nucleoli may be present in some of the nuclei which contain small inclusion bodies. The larger inclusions tend to lie in a more or less central position, although fairly large bodies may be excentrically located. A single inclusion is often found in a nucleus, but some nuclei contain two or three fairly large inclusions; and several very small ones varying in size may be seen in a single nucleus, which may or may not contain a larger inclusion body in addition to the smaller ones. Occasional slightly enlarged nuclei are found which may be almost filled with minute particulate acidophilic inclusions (plate I, fig. 1).

Most of the inclusions are acidophilic in staining properties. In thin paraffin sections of tissue fixed either in formalin, sublimate-alcohol, or in Zenker-formalin solution without acetic acid, the majority of the

inclusions are strongly colored by eosin when the sections are properly stained with haematoxylin and eosin or with eosin and methylene blue. Some of the larger inclusions may look purple, however, and in haematoxylin and eosin preparations the center of the larger inclusions may be less intensely stained than the periphery or may not stain with either the acid or basic dye. In sections stained with phloxin and methylene blue or haematoxylin the larger inclusions show a deeply stained center and paler narrow periphery. Phloxin stains the inclusions brilliantly, and clearly demonstrates the smaller forms. In acid fuchsin and methylene blue, and when stained by Giemsa's method, the inclusion bodies are red or pink. They give negative staining reactions for fat (Scharlach R), calcium (Von Kossa's silver stain), iron (Prussian blue reaction), lead (30), and for thymonucleic acid (Feulgen reaction). They are not doubly refractive when viewed under the polarizing microscope, and in frozen sections of fresh unfixed tissue the larger inclusions appear to be hyaline and homogeneous.

The nuclei in which inclusion bodies are found in the kidney show very pronounced alterations in size, shape, and in the content and distribution of basophilic chromatin granules. The nuclei increase in size, and may become two or three times larger than normal. Most of them, however, are but moderately enlarged. Elongated or ovoid forms are found, and some nuclei are curiously misshapen and irregular in form. The basophilic chromatin granules increase in some nuclei and a few large irregular nuclei are found, almost solidly filled with deeply stained, closely packed threads and granules of chromatin. Such hyperchromatic nuclei are uncommon, however, and when found they may show either a single large purplish inclusion or a small acidophilic inclusion body surrounded by a narrow clear area. In many of the moderately enlarged nuclei chromatin granules collect both along the periphery of the nuclear membrane and also about the margin of the inclusion, leaving a clear zone with few chromatin granules and threads between the inclusion body and the periphery of the nucleus. The final step in the formation of the inclusions is apparently represented by an occasional large irregular body which completely fills a nucleus and is surrounded by a thin rim of solid black chromatin closely applied to the inclusion (plate I, fig. 16). Cells with nuclei of this character are evidently necrotic.

The cytoplasm of the epithelial cells in the kidney whose nuclei

contain inclusions is also abnormal. Some cells are distinctly enlarged. Globules of neutral fat may be stained in the cytoplasm. The cells with large hyperchromatic nuclei may look coagulated and some of them are evidently necrotic. Many cells in the cortical rays show thin cytoplasm which is basophilic, and the corresponding tubules look widened. In one of the cases there is fairly widespread calcification of necrotic tubular epithelium; and aside from frankly necrotic cells which can be found in each case, occasional mitotic figures are plainly visible, indicating regeneration of tissue. As a consequence of these changes very small tubules with narrow lumina lined with new cells may eventually be left in the cortical rays. In some of the cases such atrophied tubules are found to be numerous, and are associated with some scarring and round-cell infiltration of the tissue between the tubules of the cortical rays.

The inclusion bodies in the liver cells of children are practically identical in appearance with those found in the kidney. They are less numerous in the liver in most cases, and only a few are found in three of the cases in which the inclusions are plentiful in the kidneys. In general the inclusions in the liver cells are small compared with the numerous larger inclusions in the tubular epithelium of the kidney. The nuclei of the affected liver cells show less marked alteration in size and shape than the damaged nuclei in the kidney. There are, however, many abnormal nuclei, with and without inclusions, and large "empty" nuclei with thick, crinkled, deeply stained nuclear membrane are especially conspicuous in the paraffin sections. In most of the cases there are abundant globules of fat in the liver cells throughout the lobules. Occasional necrotic cells with pyknotic nuclei and cytoplasm are found in some of the cases, and in the majority there is evidence of destruction of a few periportal liver cells together with slight chronic inflammatory reaction and scarring in each portal area. In a few cases there is, in addition, slight proliferation of bile ducts. These changes, extending along the smallest bile ducts, accentuate the liver lobulation.

Microscopical sections of the liver and kidney of 50 children who died with tuberculous meningitis, and the sections of liver and kidney from 55 cases of acute poliomyelitis were examined for similar intranuclear inclusions. A few inclusion bodies were found in the kidney in

three cases of poliomyelitis and in one case of tuberculosis, and they were present in the liver in one of the cases of poliomyelitis. The inclusions which were found in these four controls occurred in the tissues of children, and were identical in appearance with the intranuclear bodies of lead poisoning. It is probable that they were produced by lead, for it seems evident that children with pica may ingest abnormal amounts of lead and may die from various diseases before the symptoms of lead poisoning develop. Typical intranuclear inclusions were also found in the liver and kidney of one adult, an enamel worker dying from lobar pneumonia. This patient was anaemic (haemoglobin, 42 per cent), and although he apparently had no clinical symptoms of lead poisoning, eight cases with definite clinical symptoms had recently occurred among his fellow employees. These cases suggest that intranuclear inclusions may be produced before clinical symptoms of lead poisoning are detected.

The tissues of four individuals exposed to lead for long periods have also been examined and they show very few or no intranuclear inclusion bodies. A few inclusions are present in the kidneys of two lead workers who died with chronic nephritis and were looked upon as examples of chronic lead poisoning. A third similar case, in a lead worker with chronic nephritis, showed no inclusion bodies in the tissues. In the fourth case, in a girl of six with terminal lead encephalitis, although the blood lead was high (0.2 to 0.5 mgm. per cent) for three years, only a few small inclusions were found in the kidney. In the liver in this case, however, there are numerous intranuclear inclusions of typical appearance.

EXPERIMENTAL LEAD POISONING

Intranuclear inclusion bodies may be readily produced in the kidneys and occasionally in the liver of guinea-pigs, mice and rats by adding lead to the food of the animals. The inclusions produced experimentally are identical in microscopical appearance with the nuclear inclusions in liver and kidneys of children poisoned by repeatedly nibbling the paint from articles of furniture or other objects. Lead poisoning in animals and in children causes more pronounced changes in the kidneys than in the liver; and in the experimental animal, as in man, in addition to the intranuclear inclusion bodies, there are marked

changes in the size and shape of the affected nuclei, in the quantity and distribution of basophilic chromatin, and in the cytoplasm of the damaged cells.

Attempts have not been made to determine the minimal quantity of lead necessary to produce intranuclear inclusion bodies within a given period. A few cubic centimeters of a 10 per cent suspension of lead carbonate in water were mixed with the food (Domino Rabbit Pel-ets) and given daily to 24 young white rats. The diet was taken with evident distaste and with some irregularity. Typical intranuclear inclusion bodies were found microscopically in the kidneys of 20 of the 24 rats, and were present in some liver cells of 8 rats. Some of the rats were killed at intervals, and others died after feeding for longer periods on the diet with added lead.

No inclusion bodies could be found in the tissues of three rats which were killed at the end of four days. Three rats were killed at weekly intervals for twenty-one days, and in the kidneys of these nine animals there were a few intranuclear inclusions. In the kidneys of 10 rats which lived from one to two months on the diet with added lead there were very marked changes in the tubular epithelium of the kidneys, with widespread patchy necrosis and regeneration of cells; and abundant intranuclear inclusion bodies were found which in every way resemble the inclusions in the kidneys of the children as described above. The tissues of 24 control rats, killed at the end of two months, showed no inclusion bodies.

DISCUSSION

It is interesting to compare the inclusions caused by lead poisoning with other inclusion bodies, for the intranuclear inclusions caused by virus infections differ sharply in morphology among themselves, and they differ from each other as noticeably as lead inclusions vary in appearance from some virus inclusions. Apparently the intranuclear inclusions of certain virus infections are stamped in each case by particular characteristics, and this is well illustrated by Cowdry's critical comparison of the inclusions which develop in the liver cells in yellow fever with other intranuclear virus inclusions (20).

It is usually said that virus inclusions are acidophilic in reaction to various stains. Some of the inclusions produced by the ingestion of lead are purplish when stained with haematoxylin and eosin, and these

evidently contain basophilic materials. Certain virus inclusions are also basophilic. Tyzzer described red and purplish inclusions in chickenpox (eosin-methylene-blue preparation) (8), and the herpes inclusions produced experimentally by Goodpasture and Teague in the cornea of the rabbit were found to be pink or purplish (31). Müller, too, found that some of the intranuclear inclusions of so-called visceral virus disease are basophilic (32). The peripheral portion of some of the lead inclusions may stain more intensely than the center or vice versa, and intranuclear inclusions exhibiting this variation in staining have been seen also in the lesions of smallpox (20).

Luger and Lauda described a series of steps or transitions by which the formation of the intranuclear inclusions of herpes may apparently be traced from the gradual accumulation of homogeneous or granular acidophilic (oxychromatic) masses scattered throughout the nucleus to the final development of a condensed, circumscribed, large inclusion body (33). At the same time the nucleus becomes hyperchromatic, and the basophilic chromatin gathers along the nuclear membrane. It is possible to assume that a somewhat similar series of transitional stages is concerned in the development of the large inclusions of lead poisoning, for some nuclei, enlarged and hyperchromatic, are practically filled with granular and drop-like inclusions; others show several or single inclusions of larger size, and in still other nuclei larger and larger inclusions are found. The larger inclusions may or may not actually be formed in this manner by the condensation of smaller bodies. When formed, however, they are apparently quite homogeneous, and in this respect are unlike some intranuclear virus inclusions. But the virus inclusions found in Borna's disease (20), and some of the intranuclear bodies of chickenpox (8) and of virus III infection (20) are also said to be amorphous and homogeneous.

The fate of nucleoli in the presence of inclusions caused by virus infection is variable, and their rôle in the formation of inclusion bodies is not clear. In lead poisoning the majority of the nuclei bearing inclusion bodies show no distinct basophilic nucleoli. Likewise in the testis of the rabbit infected with virus III, nucleoli are not usually visible in nuclei which contain typical inclusions (20). The inclusion bodies of lead poisoning are too numerous in some of the nuclei to be regarded simply as hypertrophied nucleoli.

The separation of basophilic chromatin from the eosinophilic in-

clusion body to leave a clear zone between the inclusion and the periphery of the nucleus is said to be typical of nuclei which contain inclusion bodies of type A; but the character of this change is variable.

In lead poisoning relatively clear nuclei are commonly seen in which chromatin granules tend to collect both at the periphery of the nuclei and about the margins of the red inclusions as well. Likewise in the salivary gland disease of guinea-pigs which was studied by Cole and Kuttner and proved to be caused by infection with a virus, some basophilic material remained in the relatively clear nuclei, and radiating bands of basophilic chromatin were found which extended outward from the margins of some of the inclusion bodies to the nuclear membrane (23). The inclusion bodies discovered in the salivary glands of moles, although originally described by Rector and Rector as being basophilic (19), and classified by Cowdry with type A inclusion bodies (18), are now said to be actually acidophilic inclusions surrounded by a layer of basophilic chromatin (34). The basophilic granules which are applied to the margin of some of the larger inclusions of lead poisoning are never so numerous and thick as to obscure the acidophilic inclusion.

It will be evident from these comparisons that the inclusions of lead poisoning are in general quite similar in morphology and staining properties to the inclusion bodies caused by some virus infections; and similar changes in the basophilic chromatin of the nuclei are caused by certain virus infections and lead poisoning. It may be said in general that both lead poisoning and certain virus infections produce inclusion bodies which are similar in their intranuclear position, and in their more or less acidophilic staining reactions; and both cause changes in basophilic chromatin, and in the size and shape of the nuclei, and may lead to necrosis of cells. The inclusion bodies of many virus diseases are circumscribed granular masses. In some virus diseases they are homogeneous and hyaline. Lead poisoning produces many homogeneous, hyaline inclusions, and some which are granular and loosely scattered in the nuclei.

SUMMARY

Intranuclear acidophilic inclusion bodies were found in the tubular epithelium of the kidneys and in liver cells in twenty-one cases of lead poisoning occurring in children, and similar inclusions were reproduced in the kidneys of guinea-pigs, mice and rats by adding lead to the diet of these animals.

The inclusion bodies in the liver and kidney of children, and those produced experimentally in animals are variable in size and shape. Many of them are quite large, and are round, smooth, and homogeneous in appearance. Some are plastic and assume the shape of the distorted nuclei in which they occur. Some of the nuclei contain many small granular and drop-like inclusion bodies.

Like the intranuclear inclusions of virus diseases the majority of the inclusion bodies of lead poisoning are stained by dyes such as eosin and phloxin, and they give a negative staining reaction for thymonucleic acid. It is probable that the inclusion bodies represent accumulations in damaged cells of the acidophilic material which is present in smaller amounts in normal cells.

As in virus diseases, the nuclei in which the inclusions of lead poisoning occur are increased in size and altered in shape; and the arrangement of basophilic chromatin in the nuclei is also abnormal. The quantity of chromatin is greatly increased in some nuclei. In many others the chromatin granules collect along the periphery of the nucleus and also along the margin of the inclusion body, leaving a relatively clear space between the inclusion and nuclear membrane.

The cytoplasm of the affected cells in the kidney especially is also damaged. Some cells are enlarged. Many are thin, flattened and basophilic in appearance. Some cells contain fat, especially in the liver, and in both kidney and liver completely necrotic cells are found. Evidence of regeneration of tissue in the kidneys is indicated by the presence of mitotic figures and cells with basophilic cytoplasm.

The tubules in each cortical ray of the kidney are especially damaged by lead, and in this location atrophied tubules, scars and slight chronic inflammation may be found. In most of the affected human livers, aside from fat deposits in the cytoplasm and marked changes in the nuclei of the hepatic cells, there is slight inflammation and scarring in the periportal areas, accompanied in some instances by slight proliferation of bile ducts.

TABLE I

EVIDENCE OF LEAD POISONING IN TWENTY-ONE CHILDREN

Case 1. Autopsy No. 4316. *Age:* 2½ years. Ate paint from furniture. Vomited for 1 month. Had convulsions for 3 weeks. Lead line on gums. Hgb., 50%. Red blood cells stippled. Lead line in microscopical sections of ribs.

Case 2. Autopsy No. 5940. *Age:* 3 years. History of pica. Malaise for 1 month. Convulsions for 1 day. Lead line on gums. Hgb., 60%. Stippled red blood cells. Microscopical lesions of lead encephalitis, and lead line in microscopical sections of ribs.

Case 3. Autopsy No. 7532. *Age:* 2 years. Ate paint from window sills and toys. Vomited for 1 month. Coma, nystagmus, and convulsions for 1 day. Hgb., 45%. Stippled red blood cells. Microscopical lesions of lead encephalitis and lead line in microscopical sections of ribs.

Case 4. Autopsy No. 9277. *Age:* 2 years. Ate white lead paint and died 2 weeks later. Vomited for 1 week. Convulsions for 1 day. Hgb., 45%. Microscopical lesions of lead encephalitis, and lead line in microscopical sections of ribs.

Case 5. Autopsy No. 10465. *Age:* 3 years. Ate house paint. Vomiting, strabismus, and convulsions for 1 week. Lead line on gums. Stippled red blood cells. Microscopical lesions of lead encephalitis, and lead line in microscopical sections of ribs.

Case 6. Autopsy No. 10637. *Age:* 22 months. Gnawed painted furniture for 6 months. Vomiting, constipation and drowsiness for 3 weeks. Convulsions and strabismus for 3 days. Hgb., 50%. Stippled red blood cells. Microscopical lesions of lead poisoning in brain and ribs.

Case 7. Autopsy No. 10850. *Age:* 13 months. Chewed white paint from "pen" for 4 months. Had convulsions for 2 days 1 month before death. Later, spastic paralysis, left. Right arm and head in constant motion. Hgb., 54%. Stippled red blood cells. Microscopical lesions of lead poisoning in brain and ribs.

Case 8. Autopsy No. 11482. *Age:* 21 months. Ate paint from wooden articles for 2 months. Crying and vomiting for 2 weeks. Coma, nystagmus, and convulsions for 2 days. Hgb., 65%. Lead line in microscopical sections of rib. Brain not examined.

Case 9. Autopsy No. 11766. *Age:* 2 years. Chewed clothes, paper and plaster. Vomiting for 2 weeks. Nystagmus and convulsions for 1 day. Microscopical lesions of lead encephalitis. Lead line in x-ray, and in microscopical sections of bones.

Case 10. Autopsy No. 12168. *Age:* 3½ years. Played at neighbor's house while being painted. Vomiting and abdominal pains for 3 months. Ascending paralysis and convulsions for 1 month. Hgb., 60%. Stippled red blood cells. Microscopical lesions of lead encephalitis, and peripheral neuritis. Lead line in x-ray and in microscopical sections of bones.

Case 11. Autopsy No. 13334. *Age:* 3½ years. Vomiting for 2 days. Coma, bradycardia and convulsions for 1 day. Lead line on gums. Hgb., 45%. Stippled red blood cells. Blood lead, 0.1 to 0.2 mgm.%. Microscopical lesions of lead encephalitis. Lead line in x-ray and in microscopical sections of bones.

Case 12. Autopsy No. 13698. *Age:* 2 years. Ate plaster, ashes, and paint from window sills. Vomiting for 1 month. Constipation and abdominal pain. Coma for 4 days. Convulsions for 1 day. Lead line on gums. Hgb., 50%.

Blood lead, 0.5 to 1 mgm. %. Microscopical lesions of lead encephalitis. Lead line in x-ray and in microscopical sections of bones.

Case 13. Autopsy No. 13726. *Age:* 2 years. House recently painted. Vomiting for 2 months. Nystagmus and convulsions for 2 days. Hgb., 58%. Stippled red blood cells. Blood lead, 0.5 mgm.%. Microscopical lesions of lead encephalitis. Lead line in x-ray and in microscopical sections of bones.

Case 14. Autopsy No. 13795. *Age:* 2 years. Chewed paint from dolls for 2 months. Constipation and vomiting for 2 weeks. Abdominal pains. Convulsions for 1 day. Blood lead, 0.5 mgm.%. Microscopical lesions of lead encephalitis. Lead line in x-ray and in microscopical sections of bones.

Case 15. Autopsy No. 13830. *Age:* 3 years. Sucked painted toys. Vomiting and abdominal pain for 1 month. Stupor and convulsions for 1 day. Hgb., 48%. Stippled red blood cells. Blood lead, 0.5 to 1 mgm.%. Microscopical lesions of lead encephalitis. Lead line in x-ray and in microscopical sections of bones.

Case 16. Autopsy No. 14057. *Age:* 7 years. Chewed crayon and chalk. Drowsy for 5 weeks. Vomiting and abdominal pain for 4 weeks. Coma and convulsions for 2 days. Lead line on gums. Stippled red blood cells. Blood lead, 0.5 mgm.%. Microscopical lesions of lead encephalitis. Lead line in x-ray and in microscopical sections of bones.

Case 17. Autopsy No. 14287. *Age:* 3 years. History of pica. Vomiting and drowsiness for 5 weeks. Coma, nystagmus, and convulsions for 1 day. Hgb., 62%. Stippled red blood cells. Blood lead, 0.5 mgm.%. Microscopical lesions of lead encephalitis. Lead line in x-ray and in microscopical sections of bones.

Case 18. Autopsy No. 14307. *Age:* 18 months. Ate flakes of dry paint from walls. Anorexia for 6 weeks. Vomiting for 1 week. Convulsions for 1 day. Hgb., 50%. Blood lead, 0.5 to 1 mgm.%. Microscopical lesions of lead encephalitis. Lead line in x-ray and in microscopical sections of bones.

Case 19. Autopsy No. 14336. *Age:* 19 months. Ate plaster. Constipation for 2 to 3 months. Drowsiness and vomiting for 1 week. Convulsions for 1 day. Lead line on gums. Hgb., 35%. Blood lead, 0.2 mgm.%. Microscopical lesions of lead encephalitis. Lead line in x-ray and in microscopical sections of bones.

Case 20. Autopsy No. 14352. *Age:* 18 months. Sucked indelible lead pencil and chewed paint from ice-box. Constipation for 2 weeks. Vomiting for 1 week. Convulsions for 3 or 4 days. Stippled red blood cells. Blood lead, 0.5 mgm.%. Microscopical lesions of lead encephalitis. Lead line in x-ray and in microscopical sections of bones.

Case 21. Autopsy No. 14370. *Age:* 2½ years. History of pica. Vomiting for 1 week. Convulsions for 1 day. Lead line on gums. Stippled red blood cells. Blood lead, 0.2 to 0.5 mgm.%. Microscopical lesions of lead encephalitis. Lead line on fluoroscopic examination and in microscopical sections of bones.

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PLATES

EXPLANATION OF PLATES

The figures in plate 1 are drawings which show only the nuclei of epithelial cells in the kidney and liver of a child. The nuclei were selected from a case of lead poisoning to illustrate the appearance of inclusion bodies and to show the changes in basophilic chromatin and in the form of the nuclei. The tissues were fixed in Zenker-formalin solution and stained with phloxin and haematoxylin. The drawings were made by the use of Spencer ocular 10, Bausch and Lomb objective 1.9 mm., and camera lucida. The magnification is approximately 1500. The acidophilic inclusion bodies are represented in gray. Nucleoli, basophilic chromatin, and nuclear membranes are black.

PLATE I

FIGS. 1–16 show a series of nuclei from the kidney of a single case of lead poisoning (Autopsy No. 14287). The intranuclear inclusions, represented in gray, increase more or less regularly in size. It is theoretically possible that the larger inclusions are formed by coalescence of smaller ones. The basophilic chromatin in the nuclei is irregular in distribution. Some is collected along the margin of the nuclear membrane and particles of chromatin adhere to some of the inclusions.

FIG. 1 shows a slightly enlarged nucleus which contains numerous small granular inclusions in gray, and only a few black basophilic granules of chromatin which are seen towards the periphery of the nucleus. Probably an early stage in the nuclear change.

FIG. 2 shows a nucleus in which there are two small round inclusions surrounded by a clear zone.

FIG. 3. The nucleus contains four inclusions a little larger than those in figures 1 and 2. They are irregularly scattered in the nucleus.

FIG. 4. Near the center of the nucleus there is a mass consisting of six acidophilic inclusions crowded closely together. The nucleus looks clear and the basophilic chromatin is concentrated towards the nuclear membrane.

FIGS. 5–12 show enlarged nuclei and some which are very abnormal in size and shape. They contain few or numerous inclusions varying in size. Many are round drop-like bodies. Some are irregular in form, and in two nuclei (figs. 5 and 7) there are numerous small granular and larger round inclusions.

FIGS. 13–15 show distorted nuclei which contain single large acidophilic inclusions of irregular form. Basophilic chromatin is collected along the edge of each inclusion and also at the periphery of the nuclei. Strands of chromatin may be seen extending from the inclusions to the margins of the nuclei.

FIG. 16. The nucleus is entirely filled by an irregular homogeneous inclusion which is surrounded by a thin black rim of chromatin.

FIGS. 17–20 show four nuclei from the liver of one case of lead poisoning (Autopsy No. 11766). In figure 17 two black basophilic nucleoli may be seen at opposite poles of a larger acidophilic inclusion body.

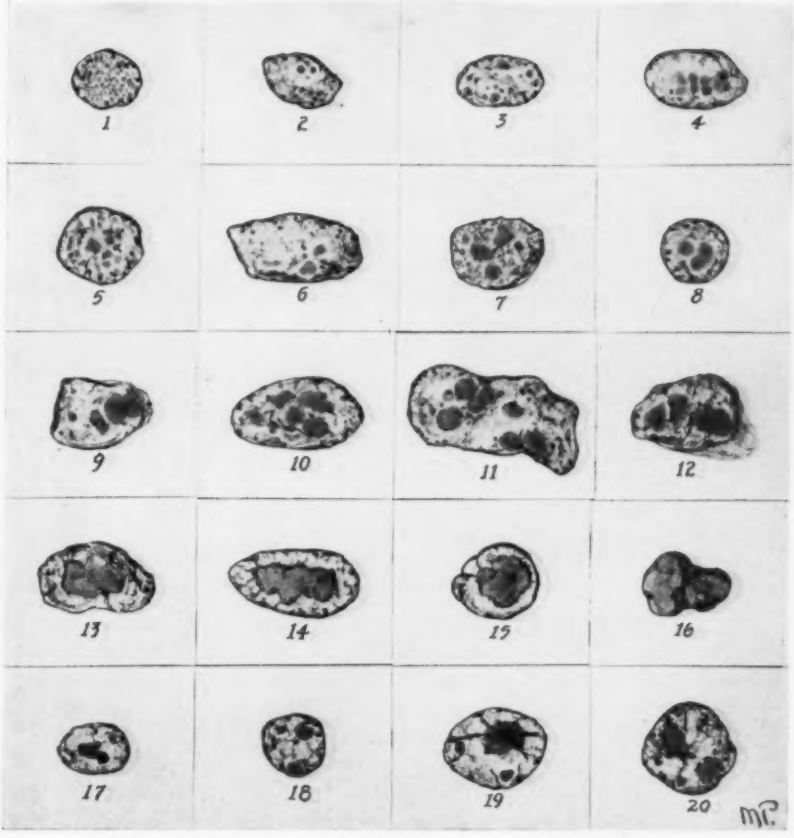
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PLATE II

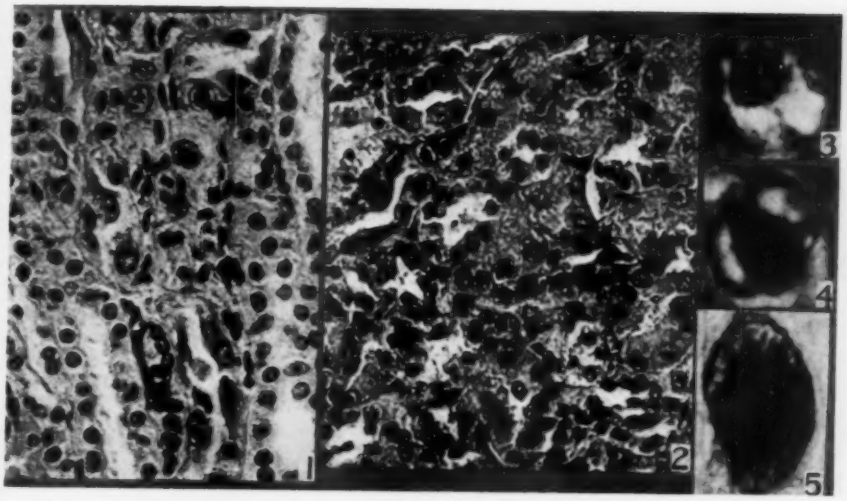
(Photographs by Mr. Milton Kougl)

FIG. 1. Autopsy No. 11766. H. & E. × 390. Inclusion bodies may be seen in several enlarged nuclei of epithelial cells in a cortical ray of the kidney. There is a clear zone between each inclusion body and the periphery of the nucleus.

FIG. 2. Experimental lead poisoning. Microscopical section of kidney, Rat 2, H. & E. × 390. The inclusions in the enlarged nuclei of tubular epithelium resemble those in the human kidney, figure 1.

FIG. 3. Kidney of rat 75-12-R-11, H. & E. × 1200. A single intranuclear inclusion is shown in the kidney of a rat given lead poisoning.

FIG. 4 (Autopsy No. 14287) and FIG. 5 (Autopsy No. 14057). H. & E. × 1200. Photographs of single intranuclear inclusion bodies in renal tubular epithelium from two cases of lead poisoning in children.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OBSERVATIONS ON THE PATHOLOGICAL CHANGES IN SUPRARENALECTOMIZED DOGS, WITH PARTICULAR REFERENCE TO THE ANTERIOR LOBE OF THE HYPOPHYSIS

A Comparison with Addison's Disease[1]

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The contrast between the pathological changes observed in the hypophysis in Addison's disease, whether due to suprarenal cortical atrophy or due to tuberculosis, together with the absence of hypophyseal changes in the suprarenalectomized dog, which have been found in the following study, suggests that suprarenal cortical atrophy may be due primarily to changes in the anterior lobe of the pituitary or, at any rate, that the same process may be responsible for the change in both glands.

Most of the earlier reports on the pathological changes in experimental suprarenal insufficiency describe the lesions that occur in acute failure and cannot be interpreted as changes due to the absence of the hormone excreted by the suprarenal cortex. The survival periods of the animals were too short to give an accurate index to the changes that resulted from the absence of the glands. Marine and Bauman (1), in 1922, found haemorrhage and ulcers in the stomach and atrophy of the pancreas in suprarenalectomized rabbits that previously had been thyroidectomized and had survived the removal of the adrenal glands for 14 to 63 days. Banting and Gairns (2) described extreme congestion of the liver, spleen, kidneys, pancreas, omentum, and intestines. Superficial ulcers in the stomach and duodenum, and marked enlarge-

[1] I wish to extend my thanks to Dr. Frank B. Kindell of the Department of Pathology who made the autopsies on the earlier dogs and who has generously permitted me to make use of his notes and materials.

ment of the lymph nodes, spleen and thymus were also evident. The experimental animals were dogs, whose survival periods after operation varied from 24 to 150 hours. Rogoff and Stewart (3), in 1926, reported the findings in dogs that had survived suprarenalectomy for an average of 3 to 8 days. The pathological changes noted were congestion of the pancreas, spleen, stomach and intestines, and enlargement of the lymph nodes. Yonkman (4) described enlargement and congestion of the spleen and congestion of the pancreas in dogs.

MacMahon and Zwemer (5), in 1929, working with cats as experimental animals that lived 100 to 300 hours after bilateral suprarenalectomy, report: "Histologic changes which appear to be constantly associated with adrenal insufficiency are confined to the kidney, lymphoid tissue throughout the body, thyroid and testes." The renal lesions were characterized by large amounts of fat in the convoluted tubules. The lymphoid tissue was described as being markedly hyperplastic. There was proliferation of plasma cells and the germinal centers were large and filled with lymphocytes. In the thyroid the follicles were distended with colloid; the epithelium was low cuboidal or slightly flattened. The interstitial cells of the testes were increased in size and number.

The anterior lobe of the hypophysis secretes a hormone that produces definite alterations in the structure of the adrenal cortex. After extirpation of the hypophysis, atrophy of the adrenal cortex takes place (6, 7, 8). On the other hand, if an intact animal receives an extract of the anterior hypophysis, according to Emery and Atwell (9), the adrenal cortex will hypertrophy.

It has not, as yet, been satisfactorily demonstrated that the hormone of the adrenal cortex has a definite effect upon the anterior lobe of the hypophysis. Most observers, however, agree that there is a striking reduction in the basophilic cells and slight reduction in the eosinophilic cells in Addison's disease. Kiyono (10), in 1926, described the pathological findings in 2 cases of Addison's disease, both of which showed a definite decrease in the number of basophilic and eosinophilic cells in the anterior lobe of the pituitary. Kraus (11, 12, 13) reported a reduction in the basophilic and eosinophilic cells of the anterior lobe in patients dead of Addison's disease. In one case no change from the normal was found. Berblinger (14) likewise de-

scribed a reduction in the number of basophils, and called attention to the fact that many of the cells contained pycnotic nuclei. Hewer (15), in 1923, was the first to report the fact that there is a reduction of the large basophils in the anterior lobe in Addison's disease. Terplan and Sanes (16) reported the same findings in one case of Addison's disease. Brenner (17), in 1928, recorded 5 cases of atrophy of the suprarenal cortex and mentioned 2 cases in which the eosinophilic cells of the anterior lobe of the hypophysis were preponderant. One of his cases showed a great increase in the basophilic cells.

Crooke and Russell (18) find a reduction in the eosinophils with extreme paucity of basophils. They also describe three distinct types of basophilic transitional cells in the anterior lobe of the hypophysis which they think are characteristic of Addison's disease. Messen (19) described two cases of Addison's disease. One patient that died early in the course of the disease showed marked wandering of the basophilic cells into the posterior lobe. The anterior lobe was normal. In the other case there was atrophy of the pars intermedia and diminution of the basophils and large eosinophils in the anterior lobe. The small eosinophilic cells were predominant.

The effect of the suprarenal cortex upon the morphology of the anterior lobe of the hypophysis in experimental animals is confusing. Martin (20), working with white rats, says: "Suprarenalectomy . . . causes a decrease in the size and staining reaction of the oxyphil cells of the anterior lobe of the pituitary gland. The effect on the basophils is not constant." Moehlig and Bates (21), using dogs as experimental animals, report a marked increase in the basophilic cells. Corey and Britton (22), by injecting extract of the adrenal cortex into intact white rats, produced hypertrophy of the anterior lobe of the hypophysis and a marked increase in the eosinophilic cells. Shumacker and Firor (23), in one dog that had been allowed to develop chronic adrenal insufficiency, found changes in the anterior lobe of the hypophysis comparable to those described for Addison's disease. Grollman and Firor (24) likewise describe paucity of basophilic cells, a reduction in eosinophils and congestion of the anterior hypophysis, and in addition describe atrophy of the reproductive organs and of the thyroid.

METHODS AND MATERIALS

The animals used in this study were suprarenalectomized adult mongrel dogs, and consisted of 4 females and 21 males. Every dog was tested for complete removal of the suprarenal glands by withdrawal of cortical extract and sodium chloride, and in each instance signs and symptoms of acute suprarenal insufficiency developed. In addition to this precaution, a careful search was made for any remaining cortical tissue when the autopsy was performed. The maintenance and care of the suprarenalectomized animals have been described in a previous report from this laboratory (25).

Two dogs, no. 122 and no. 132, were bled to death while under ether anaesthesia, and the autopsy was performed immediately. The autopsies on the other dogs were performed as early as possible after death, in order to prevent autolysis of the tissues. In several instances autolysis was considerable and therefore the material is not included in this report.

The tissue was fixed in Zenker-Formol solution, and the paraffin sections were made and stained with haemotoxylin and eosin. The hypophysis was removed intact and fixed in Zenker-Formol solution. All sections were cut in the sagittal plane, and the paraffin sections were stained by the Mann Stain as recommended by Kindell (26). Only one section was studied from the first 15 hypophyses so obtained. On the last 10 a somewhat different technique was followed in that sections were made and studied from four different levels of the hypophysis; however, these also were cut in the sagittal plane. Tissue was also fixed in 10 per cent formalin. Frozen sections were made on the formalin fixed tissue and stained with Scharlach R.

No accurate differential count was made of the cells in the anterior lobe of the hypophysis; however, in each section 600 cells were counted from representative fields. The oil-immersion lens (magnification 1000x) was used in making the counts.

Sections from the hypophysis of four normal dogs were used as a control in this study.

RESULTS

The animals survived for periods of 11 (Dog F-4) to 689 days (Dog 70) following removal of the adrenals.

Nutrition: In the animals that survived several months the nutrition was uniformly good. When emaciation occurred the condition was due either to infection or anorexia.

Heart: Small areas of necrosis and foci of plasma cells were found in the myocardium of Dog F-15; however, this animal had received injections of a commercial extract, which later was found to produce identical lesions in a normal dog. The right and left ventricles of Dog 70 contained numerous worms (strongylus gigas) and this fact might explain the small foci of plasma cells found, as they were located immediately beneath the endocardium. There were scars on the myocardium found in Dog 132 which were probably due to repeated heart punctures.

The remainder of the animals showed no change from the normal.

Lungs: Lobular pneumonia was found in four dogs. Edema in varying degrees was present in all dogs that died in acute insufficiency, with circulatory failure. Dog 123 received intravenous fat and died from fat emboli.

Liver: Atrophy of the central liver cells was found frequently, occurring in 15 of the 25 dogs. Dog 70 showed slight scarring of the central portion of the lobule, in addition to the atrophy.

Stomach and Intestines: Seventeen dogs showed some type of lesion in the stomach or duodenum. The lesions occurred only when the animal died in acute insufficiency, and consisted of a marked congestion of the mucosa and occasional haemorrhage. The dogs which survived the longest and died from other causes but had repeatedly been subjected to the withdrawal of cortical extract showed small healed ulcerations in the mucosa.

Kidneys: Eight of the dogs showed either acute pyelitis or scars and foci of cells, resulting from an old infection. In view of the repeated unsterile catherization it is surprising that infection was not present more often.

Abnormal accumulation of fat in the tubules was present in only one instance (Dog W-13).

Spleen: The spleen showed no consistent change. In Dogs W-13 and 70 there were haemorrhages into the Malpighian bodies. There was a large abscess at the hilum in Dog H-1.

Lymph Nodes: In only the animals that died of infection was there any change noted.

Bone marrow: There was active blood formation, without evidence of over-activity, in all sections studied.

Skin: The skin was normal throughout with no increase in the pigmentation.

Prostate: In the 21 male dogs reported here, 7 showed acute or chronic prostatitis. There was no evidence of atrophy or hypertrophy of the prostate.

Testes: Dogs F-6 and W-13 were the only male dogs in the entire series that did not show active spermatogenesis. Infection was noted in both animals and also in Dog 132, who showed active spermatogenesis. The interstitial cells of Leydig were normal in morphology and number.

Ovary: Four female dogs are included. Two of these showed corpora lutea and in the other two only follicles were present. There was no evidence of atrophy.

Thymus: In only one dog (No. 123) was the thymus found to be enlarged, weighing 12 grams. In the remainder of the animals it was either of normal size or atrophic. No change was found upon microscopic examination.

Thyroid: In 9 of the 25 dogs the epithelium was low but no other abnormality was found. The acini were well filled with colloid. Nor was there any evidence of hyperactivity in any of the dogs.

Parathyroid: The parathyroid glands in Dog 70 were slightly enlarged and between the cells there were fine scars. The cells, however, appeared to be normal in every respect. There was a small cyst in one of the parathyroid glands of Dog P-6. In F-6 the cells were small and dark but otherwise appeared normal.

Pancreas: There were no consistent changes in the pancreas. Dog P-2 showed

a few scattered, hyaline capillary thrombi. Dogs 110, 123, 145 and 154 showed some distention of the veins with blood. No haemorrhages were seen, however.

Hypophysis: The posterior lobe showed no change in any of the sections. In Dog F-15 there was a projection of basophilic cells into the posterior lobe. In the anterior lobe of Dogs P-10 and H-1 there were small cysts filled with bluish staining material. In one of these (P-10) it was lined with cuboidal epithelium and in the other (H-1) with high columnar epithelium. These cysts did not compress any of the surrounding cells or tissues, nor did they show signs of malignancy. There were no symptoms produced by the cysts before death of the animal.

The veins of the anterior pituitary were distended in seven of the dogs. These animals died in acute insufficiency, with low plasma sodium and chloride concentration, haemoconcentration and other symptoms of shock.

The individual type cells of the anterior lobe of the suprarenalectomized dogs did not differ in number from those of four normal dogs. While only 600 cells were counted from representative fields, the relative percentage of the different cells corresponds roughly with Rasmussen's (27 and 28) figures for normal human hypophyses. An attempt was made to correlate the number of basophils with the length of survival after removal of the adrenal glands. In reviewing the per-

TABLE 1

	BASOPHILS	EOSINOPHILS	CHROMOPHOBES
Highest	16% (dog 110)	47% (dog 70)	60% (dog 122)
Lowest	2.5% (dog W-13)	31% (dog 129)	40.1% (dog 132)
Average, 4 normal dogs	12.1%	33.7%	54.2%

centage of the different cells, it was found that no such correlation could be made, since frequently an animal that survived the operation only a relatively short period would have a few basophils, while, on the other hand, an animal that survived the operation for several months would show a considerable number of basophilic cells. For example, Dog 116 was maintained on potent cortical extract for a period of 21 days and died following a glucose tolerance test. The percentage of basophils in the anterior lobe was found to be 2.7. On the other hand, Dog 129 was maintained by the administration of sodium bicarbonate and sodium chloride without cortical extract for a period of 164 days. The basophils in the latter dog were 14 per cent.

The reverse is shown in table 1, in which it is seen that the anterior lobe of the hypophysis of Dog W-13, that survived 360 days following the removal of the adrenal glands, contained 2.5 per cent basophilic cells, while Dog 110 survived only 26 days and showed 16 per cent basophils in the anterior lobe. The percentage of basophilic cells for all of the animals varied between 2.5 and 16 per cent. Tables 2 and 3 show that the relative number of cells is the same for the dogs not treated with cortical extract and for those animals that were maintained with adequate doses of cortical extract.

The eosinophils in all the sections were likewise present in normal numbers and there was no change from the normal morphology. Only rarely were pycnotic nuclei found in these cells.

TABLE 2

Dogs surviving long periods without cortical hormones

DOGS	BASOPHILS	EOSINOPHILS	CHROMOPHOBES
	per cent	*per cent*	*per cent*
*70 (Repeatedly)	6.4	47.0	46.6
110 (17 days)	16.0	40.1	43.9
*122 (103 days)	8.1	31.9	60.0
123 (32 days)	9.6	38.2	52.2
129 (164 days)	11.3	31.0	57.7
*132 (150 days)	14.3	45.6	40.1
*145 (8 days)	4.7	38.0	57.3

Four sections studied of each hypophysis, 600 cells each.

* These animals were receiving cortical extract at the time of death.

TABLE 3

Dogs that were treated with cortical hormone

DOGS	BASOPHILS	EOSINOPHILS	CHROMOPHOBES
	per cent	*per cent*	*per cent*
4	14.2	34.7	51.1
P-2	7.6	44.3	48.1
P-4	11.0	42.4	46.6
Ad-10	5.2	40.2	54.6
Ad-11	11.2	32.8	56.0
P-6	13.0	39.8	47.2
P-5	3.4	46.0	50.6
5-8	8.1	44.2	47.7
F-4	7.5	37.6	54.9
P-10	12.0	32.0	56.0
F-6	14.2	38.1	47.7
F-7	10.9	43.1	46.0
W-13	2.5	45.8	51.7
H-1	9.4	34.6	56.0
F-15	14.6	39.0	46.4
*116	12.2	32.6	55.2
*151	11.3	41.3	47.4
*154	4.6	37.4	58.0

* Four sections of each hypophysis studied, 600 cells each.

In all of the sections studied no difference could be detected in the suprarenalectomized and the normal dogs, either from the morphology of the anterior lobe as a whole or the characteristics of the cells or the number of the individual type cells.

Table 1 shows the variation in the percentage of the different types of cells found in the anterior hypophysis of the suprarenalectomized dogs. Average cells of four normal dogs are shown in the lower line.

DISCUSSION

The only pathological change that can be predicted with any degree of certainty in bilateral suprarenalectomized dogs is found in the stomach or intestines. This change consists of old healed ulcers, or, in those dogs that die while in acute adrenal failure, marked congestion of the mucosa. It is thought that the lesions are due not to the lack or absence of the hormone of the adrenal cortex *per se*, but to the secondary physical and chemical changes that occur in the blood. Those changes are: low blood pressure, haemoconcentration, impaired circulation, lowered oxygen consumption, decrease in the plasma sodium and chloride concentration and an increase in the plasma potassium concentration. The physical and chemical alterations in the circulating blood and in the tissues are, within themselves, enough to explain the congestion of the various organs, as described by the earlier workers (1, 2, 3, 4, and 5).

MacMahon and Zwemer (5) described large amounts of fat in the convoluted tubules of the kidneys. This change was not constant in our series of dogs, and was not considered important, since it occurred with the same frequency in dogs whose adrenal glands were intact.

Koelsche and Kendall (30) report that the thymus was greatly enlarged in five suprarenalectomized dogs. The largest one reported by them weighed 80 gms. Enlargement of the thymus was not observed in any of the animals included in this report. The largest was found in Dog 123 and weighed 12 gms. This animal survived suprarenalectomy for 90 days. In Dog 70, the survival period following the removal of the suprarenal glands was 689 days; the thymus weighed 5.3 gms. Dr. Kendall (31) informs me that the dogs with which he is working require considerably more hormones than were given the dogs in our laboratory. It is suggested that the fact might explain the discrepancy observed.

Atrophy of the cells surrounding the central veins of the liver lobules was present in 15 instances, and in each case the animal died in acute suprarenal insufficiency. It is thought that the atrophy is due to cir-

culatory failure and anoxemia, and is comparable to the chronic passive congestion of the liver occurring in congestive heart failure.

The anterior lobe of the hypophysis secretes a hormone, or hormones, the absence or over-production of which causes pronounced anatomical changes in the adrenal cortex (6, 7, 8, and 9). It has not been definitely established that the adrenal cortical hormone exerts any influence upon the anterior lobe of the hypophysis sufficient to produce anatomical alterations in experimental animals. Corey and Britton (22) did produce hypertrophy of the anterior lobe in white rats, but their work has not been confirmed. Shumacker and Firor (23), and Grollman and Firor (24) observed that in "chronic adrenal insufficiency" there is a reduction in the number of basophils, a slight decrease in the eosinophils, and an increased vascularity of the anterior lobe of the hypophysis. We observed none of the lesions described by these authors. The only change from the normal was found in those dogs that died in acute suprarenal insufficiency and consisted of dilatation of the veins of the anterior lobe of the hypophysis. The dilatation of the veins was not confined to the anterior lobe of the hypophysis but was present in all of the organs.

Criticism may be directed toward the fact that "chronic adrenal insufficiency" did not exist in our dogs and for that reason the condition is not exactly comparable to that reported by Grollman and Firor. On the other hand, several animals in our series were maintained in an excellent state of health by the administration of sodium bicarbonate and sodium chloride, without the administration of cortical extract (29). This was true of dog 129 which received no cortical extract for 164 days preceding death; dog 132 was maintained for several periods of 30 days or longer, on one occasion for a period of 150 days, without cortical extract. Dog 122 was maintained in good condition for 103 days by the use of sodium chloride and sodium bicarbonate, without cortical extract. In these animals, as well as those maintained in a state of good health by the injection of adequate amounts of cortical extract, no alteration could be found in the anterior lobe of the hypophysis. Since these animals did not receive hormone, it must be concluded that in this series of experiments the lack of adrenal cortical hormone had no effect that could be demonstrated, morphologically, upon the anterior lobe of the hypophysis.

It is suggested, therefore, that the profound changes in the dog described as characteristic of adrenal extirpation are due to the disturbed water and salt metabolism combined with circulatory failure.

Dr. W. G. MacCallum of the Department of Pathology has generously permitted me to study sections of the hypophysis from 7 cases of Addison's disease. The fixation and staining technique employed in the preparation of these sections was the same as that described above for the dog. In three cases, 10322, 10718, and 12343, the sections were cut in the sagittal plane. Sections from two levels were studied in cases 10322 and 12343, but from only one level in case 10718. In four cases, 14363, 14518, 14591, and 14227, the sections were made in the horizontal plane. Three sections were studied in case 14518 and 14363, while only one section was studied in the other

TABLE 4

AUTOPSY NUMBER	ETIOLOGY	BASOPHILS	ABNORMAL CELLS OF CROOKE AND RUSSELL
14,518	Atrophy	Marked reduction	Present, large number
14,227	Atrophy	Marked reduction	Present
12,343	Atrophy	Marked reduction	Present
14,591	Tuberculosis	Slight reduction	Not seen
14,363	Tuberculosis	Slight reduction	Not seen
10,718	Tuberculosis	Normal	Not seen
10,322	Tuberculosis	Normal	Not seen

two cases. No differential counts were made in studying the human hypophysis, but a careful study was made of each section.

Table 4 summarizes the findings in the cases of Addison's disease. It will be seen that, in the cases where cortical atrophy is present, there was a reduction of the number of basophilic cells and, in addition, scattered throughout the anterior lobe, there were basophilic cells that showed agglutination of the granules and vacuolization. These changes have been described by Crooke and Russell as being typical of Addison's disease. Two of the cases of tuberculosis of the adrenal cortex exhibited no change from the normal, while in two there was a slight reduction in the number of basophilic cells. Abnormal basophils were not seen in those cases.

The eosinophils and chromophobes were normal in number and morphology. The posterior lobe was normal in all cases studied.

There was no marked wandering of cells into the pars intermedia in any of the cases.

From a study of the anterior lobe of the hypophysis in suprarenalectomized dogs and humans with Addison's disease, it became apparent that in the two conditions, a distinct difference exists in the morphology of this structure. It also is suggested, although by far too few cases have as yet been studied, that an actual difference exists between the cases of Addison's disease due to cortical atrophy and those caused by tuberculosis of the adrenal gland. No change in the basophile cells of the anterior lobe is found in the suprarenalectomized dog, and practically no change in the cases of Addison's disease in which the suprarenal cortex has been destroyed by tuberculosis. On the other hand, there is a reduction in the number of normal basophils, and occurrence of abnormal basophilic cells in those cases where cortical atrophy is found. This suggests very strongly that Addison's disease is primarily a disease of the anterior hypophysis, and that the absence of the adrenotrophic hormone secreted by this structure causes the adrenal cortical atrophy, which, in turn, is responsible for the clinical picture of Addison's disease.

SUMMARY

1. A detailed study of the material obtained at autopsy from 25 suprarenalectomized dogs is reported.

2. A comparison is made between the anterior lobe of the hypophysis from suprarenalectomized and from normal dogs. No histological difference can be determined.

3. There are no constant and characteristic pathological lesions found in dogs after total extirpation of the suprarenal glands. It is believed that the symptoms and changes found during life are due to the disturbed electrolyte and water metabolism together with the impaired circulation that occurs in the animals after the suprarenal cortex has been removed.

4. Sections of the hypophysis from 7 cases of Addison's disease have been studied. Three cases of cortical atrophy showed a reduction in the number of basophils, and the appearance of abnormal basophilic cells. Four cases of tuberculosis of the suprarenal glands showed no reduction in the number of basophils.

5. It is suggested that Addison's disease, when caused by cortical atrophy, begins primarily in the anterior lobe of the hypophysis.

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POLYURIA AND POLYDIPSIA (DIABETES INSIPIDUS) AND GLYCOSURIA RESULTING FROM ANIMAL EXPERIMENTS ON THE HYPOPHYSIS AND ITS ENVIRONS

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Two decades of intensive clinical, pathological and experimental studies have failed to solve the mystery of diabetes insipidus, *i.e.*, either the manner or the exact site of its production. Although there are those who still regard this disturbance as one of primary renal origin, there can now remain little doubt that the causative lesion is in the brain and that any changes that may occur in the kidney are secondary. The great number of necropsies revealing lesions in the brain makes this statement indisputable. The leading theories at the present time may be summed up as follows:

(1) The disturbance is of hormonal origin and the hormone arises in the hypophysis.

(2) The disease is of neurogenic origin.

(A) A center for water control is located in

(1) the hypophysis,

(2) the diencephalon

(a) the region of the tuber cinereum,

(b) the supra-optic and paraventricular nuclei.

The lines of attack intended to solve this problem have been

(1) By injection of hypophyseal extracts into patients with diabetes insipidus,

(2) By injection of extracts from tumors and other lesions (human material),

(3) By animal experimentation,

(4) By human operative procedures that serve as experiments.

Although at first glance these methods might appear to supplement each other, actually they fail to do so, and the reasons for this failure are doubtless significant. From lack of adequate control, attempts to correlate the end results of these methods have been misleading.

The principal reason for assuming that the hypophyseal secretion plays an important rôle in the production of diabetes insipidus is that when extracts of the posterior lobe (including, of course, the pars intermedia) are applied to the nasal mucous membrane, or injected hypodermically, the urinary output and the intake of fluids are reduced. Although there are many cases of diabetes insipidus that are scarcely, if at all, improved by the administration of pituitary extract, those with decided benefit are too numerous to allow us to deny the effect, when it does occur. Nevertheless, if hypophyseal extract is the all important factor in the control of water balances, it should be unfailing and not capricious in its action. And unless a satisfactory explanation of this deficit is forthcoming—and this appears improbable—a deficiency of hypophyseal hormone as the explanation of diabetes insipidus must be untenable. Moreover, if the hypophyseal hormone is the basis for the control of water balance in the body, why does the complete removal of this structure have no effect upon this function?

A second reason for the assumption of a hypophyseal factor in diabetes inspidus has been deduced from a number of cases in which a tumor has been found in the region of the hypophysis. The large size of most of these tumors makes it impossible to draw any conclusions concerning a precise point of attack in the production of diabetes insipidus. On the other hand, there are occasional small and sharply defined tumors from which fairly definite impressions are obtainable, but these must be carefully separated from the general mass of material of this type.

Since we are principally concerned in this paper with the results of animal experimentation, our impressions derived from the assets and liabilities of this method will follow the presentation of material. The experiments have been conducted exclusively on dogs. The intracranial operative attack developed by the writers and reported elsewhere[1] has been used. This approach, with a shrunken brain, affords ample room for clear observations and for any desired operative procedure, without inflicting cerebral trauma—the cause of so many misinterpretations of hypophyseal function. The animals were con-

[1] Dandy, W. E., and Reichert, F. L.: Studies on Experimental Hypophysectomy. I. Effect on the Maintenance of Life. *Bull. Johns Hopkins Hospital*, 1925, xxxvii, 1.

stantly in cages; all were studied during the fall, winter and spring; with few exceptions the ages of the puppies ranged from three weeks to three months.

In mechanically irritating the base of the brain the bent end of a probe is passed at right angles into the severed stalk of the hypophysis to a depth of 2 to 3 mm. and a longitudinal slit made by moving the probe forward to the optic chiasm and backward to the tuber cinereum. Such an incision causes injury to the so-called supra-optic and paraventricular nuclei of both sides. With the application of the cautery the entire region surrounding the hypophyseal stalk is destroyed superficially.

In order to establish controls for subsequent experiments, the intake of fluids and the output of urine were carefully measured over a period of several days before operation. The intake of fluid ranged between 100 and 1000 cc., and the output of urine between 50 and 500 cc. (Section I). We feel safe in regarding an intake of over 1000 cc. of fluid and an output of over 500 cc. of urine as evidence of polydipsia and polyuria, respectively. In a single dog, however, the intake reached 1500 and 2900 cc. and the output was proportionately high—1300 and 1450 cc. over a period of two days preceding an operation. The figures from this animal are so unusual that they should doubtless be excluded from the series of controls. The exception, however, indicates the risk of drawing conclusions from uncontrolled experiments. It, moreover, provokes the thought that perhaps the occasional instance of *permanent* polyuria and polydipsia presumably produced by an operative experiment, might in reality have given the same findings before operation.

To control still further the experimental results, four (4) dogs were anaesthetized with ether over a period of time approximating that consumed in the subsequent operative procedures; they were also given the same medicaments (morphine 64 mgm. and hypertonic salt 0.5 mgm. per kilo of body weight) that were used in the experiments. There were no appreciable effects upon the quantity of fluid and urine (Section II). Among the four controls of this group was the dog with spontaneous polyuria and polydipsia; for the following three days the measurements of fluid and urine were somewhat reduced but still remained well above the levels that we consider the outside limits of normal.

Further controls were established in two instances, *i.e.*, following the usual preliminary drugs and anaesthetization, the regular hypophyseal approach was carried out but no contact was made with the hypophyseal region. The subsequent results were entirely negative (Section III). In another group (Section IV) the region of the hypophysis was explored and the rather remote environs (not including the hypothalamus) were irritated mechanically in one instance and punctured with needles in another. There was little if any effect.

The results in terms of polydipsia and polyuria of the various experiments are most inconsistent. In almost every set of experiments the results are both positive and negative. We have analyzed these seemingly capricious results from the standpoints of age of the animals, time of the year (*i.e.*, hot or cold), difference in traumatic insults, or other factors incident to the operation, but can find no satisfactory explanation. There was always ample operative room because of shrinkage of the brain with hypertonic salt solution, and controls definitely show that the preoperative treatment plays no rôle. The animals recovered promptly from the effects of the operation, thus further disclosing the absence of cerebral pressure from traumatic oedema. It is quite obvious that, without a large series of results, experimenters might well come to diametrically opposite conclusions.

A glance at the series of charts may perhaps suggest that the experiment in which only the anterior lobe was removed (Section VII), and in which the grade of polyuria and polydipsia was much the highest, would point to a clue concerning the hidden secret; but two (one-half) of the group failed to repeat the results, although, so far as we can determine, the experiments were duplicated precisely. We have been particularly interested to know whether polyuria and polydipsia could be induced by stimulating or destroying the base after first removing the hypophysis and allowing an interval of time to elapse before the secondary procedure. From a total of 11 cases (Sections XII, XIII, XIV and XV), in only one was there an outspoken increase in the intake and output of fluids; in two there were mild increases. But although these positive results are distinctly in the minority, they nevertheless indicate that the hypophysis is not necessary for the production of polyuria and polydipsia. Camus and Roussy, Bailey and Bremer and also Houssey have long since reached this conclusion from experiments of similar character.

Following total removal of the hypophysis, polyuria and polydipsia developed in 50 per cent of the cases (6 of 12); with the additional cauterization of the base at the time of removal in 70 per cent (5 of 7), but the volumetric change was decidedly less. When the hypophyseal stalk or the body of the entire hypophysis is compressed by a tightly applied silver clip (Section X), or the stalk of the hypophysis is severed from the brain (but not removed) (Section XI), or when needles are introduced into and left in the hypophysis to stimulate it mechanically, the results are essentially the same in each set of experiments; in only 3 of 9 tests (33⅓ per cent) did a moderate grade of polyuria and polydipsia result.

Disappointing also has been our inability to induce a permanent polyuria and polydipsia such as one sees in human beings. The condition has in our experiments always been transient, lasting only two to four days in the milder grades and a maximum of 7 to 10 days in the more advanced grades. We are aware of the polyuria of long standing occasionally following experiments by Camus and Roussy, Bailey and Bremer, Towne and others, but so rarely that one is led to wonder if other factors may not be responsible—at times perhaps an unusual animal in which this condition occurs without the operation. Moreover, in some cases reported in the literature the polyuria and polydipsia began again weeks or months after the experiment—so late that the causal relationship is none too securely established.

CONCLUSIONS

1. Polyuria and polydipsia

In considering the application of canine experiments to diabetes insipidus in human beings one must bear in mind that the topographical relations of this region are entirely different—so different in fact that one may well doubt that the experimental results may be transferred with any degree of safety. And further doubt may be entertained because the polyuria induced in animals compares neither in degree nor in duration with the same symptom in human beings. In dogs the hypophysis lies snugly against the base of the brain without a distinct stalk and cells of the intermediate lobe are spread over the brain. In man the hypophysis is well isolated within a dural compart-

ment and is connected with the brain by a long stalk (2–3 cm.) that is devoid of hypophyseal tissue. In human beings operative attacks upon this region are very apt to induce permanent polyuria and polydipsia, although the temporary type also follows minor injuries.

Doubtless there is some similarity in the functions of water control dominated by this region in dogs and man, but we doubt that there is the same profound control in dogs that obtains in man. In other words, the canine experiments give us a lead but are not adequate to explain the mechanism involved in human beings. We can only conclude that there appears to be a neurogenic mechanism which can be set off by mechanical and thermal stimulation of the base of the brain and of the hypophysis as well, but that the hypophysis is not an indispensable part of it. Since polyuria and polydipsia follow injuries to the hypothalamus after the hypophysis has been removed, the conclusion is inescapable that diabetes insipidus is not due to the absence of a hypophyseal hormone. Since the paraventricular and supra-optic nuclei have unquestionably been traumatized by our mechanical and thermal injuries to the hypothalamus and with no greater effect than without such injury, we cannot believe that the center of water control is represented by these nuclei. It is our belief that only the human experiments will solve this problem.

2. Glycosuria

From the foregoing table it will be seen that both the incidence and degree of glycosuria are essentially the same in the control animals in which no attack was made upon the hypophysis or upon the base of the brain as when various operative procedures were carried on these structures. Always the urinary sugar is transient and usually it occurs only in the first specimen; occasionally it persists for 24 to 48 hours. Even in dogs without anaesthesia or medication of any kind, glycosuria will be demonstrable at times. In another somewhat larger series of dogs not included in this report, glycosuria was found in four. From these observations we see no reason to infer that the hypophysis, the hypothalamus, or any part of the base of the brain in this region, has any particular bearing on the production of glycosuria in dogs.

GUIDE FOR THE INTERPRETATION OF CHARTS

Base line indicates time (each square = a day).

Abscissa indicates maximum measurements of urine and fluid (in cc.).

Solid black = urinary output.

Enclosed clear area above solid black = fluid intake.

Cross-hatched lines = output of urine and parallel oblique lines above = intake of fluids in control animals (Charts I, II, III, IV, V and IX); after the *first* of two operations in Charts XII, XIII and XIV, and after the *second* of three operations in Chart XV. (Control readings are entered only when they may modify the interpretation of the experiment).

The *normal* intake and output is charted over a period of several days in order to insure adequate control. In subsequent experiments the readings are continued only as long as an abnormal intake or output remains. When below the normal limits only the maximum figure is charted.

This number of animals showing sugar and no sugar postoperatively is noted in the square above the fluid and urine columns in each section.

The experiments recorded in the charts are grouped as follows (Roman number on the charts):

Controls:

I. Intake or output of unoperated normal controls; 9 dogs.

II. Animals given morphia (64 mgm.) hypertonic salt solution 0.5 mgm. per kilo of body weight and ether for an hour (*i.e.*, controls without the actual operation)—4 dogs.

III. Operative exposure of hypophyseal region but nothing further done—2 dogs.

IV. Stimulation of base of brain around the hypophysis without trauma to the hypophysis or its stalk—3 dogs.

V. Total hypophysectomy—13 dogs.

VI. Total hypophysectomy and cauterization of base—7 dogs.

VII. Removal of anterior lobe only—4 dogs.

VIII. Removal of posterior lobe only—3 dogs.

IX. Introduction of needles (permanent) into the hypophysis (through both lobes)—4 dogs.

X. Compression of silver clip on hypophyseal stalk—2 dogs; and across the body of the hypophysis—1 dog.

XI. Hypophyseal stalk severed—2 dogs.

XII. (1) Total hypophysectomy and later (2) mechanical stimulation of base—3 dogs.

XIII. (1) Total hypophysectomy and later (2) application of cautery to base—3 dogs.

XIV. (1) Partial anterior and total posterior hypophysectomy, and later (2) stimulation of base—2 dogs.

XV. (1) Stalk cut; later (2) total hypophysectomy, and later (3) mechanical stimulation of base—2 dogs.

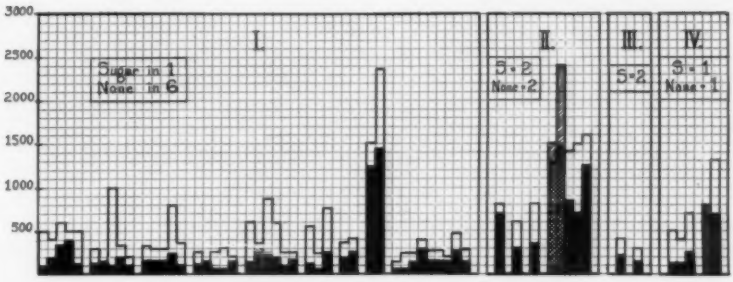

CHART 1

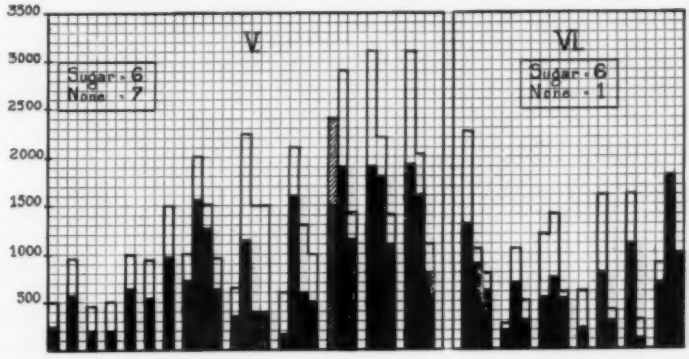

CHART 2

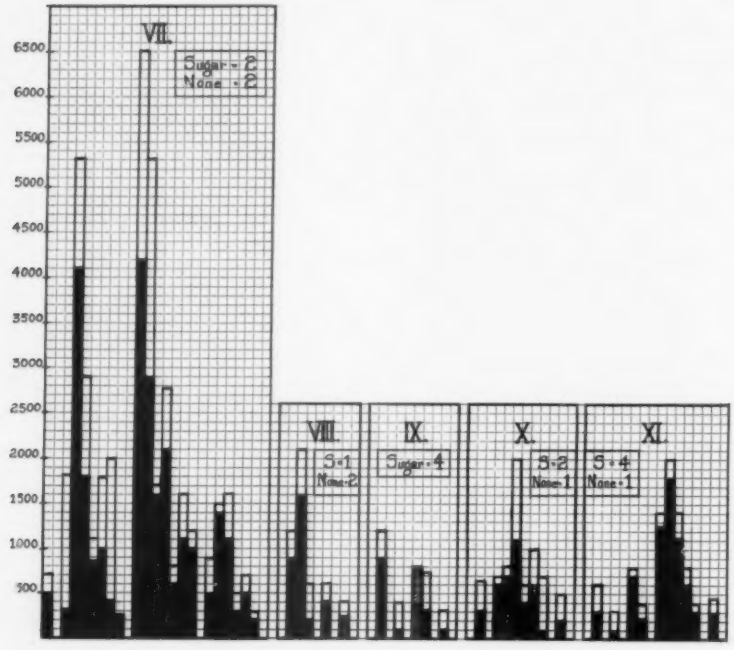

CHART 3

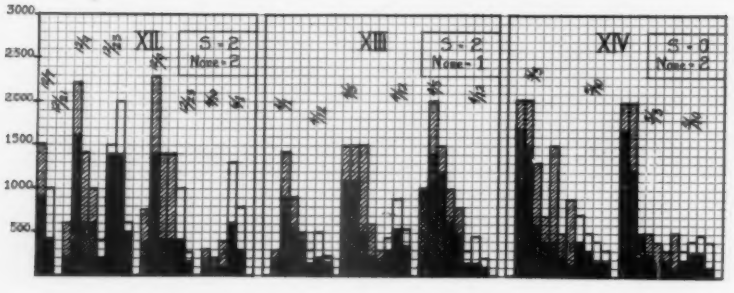

CHART 4

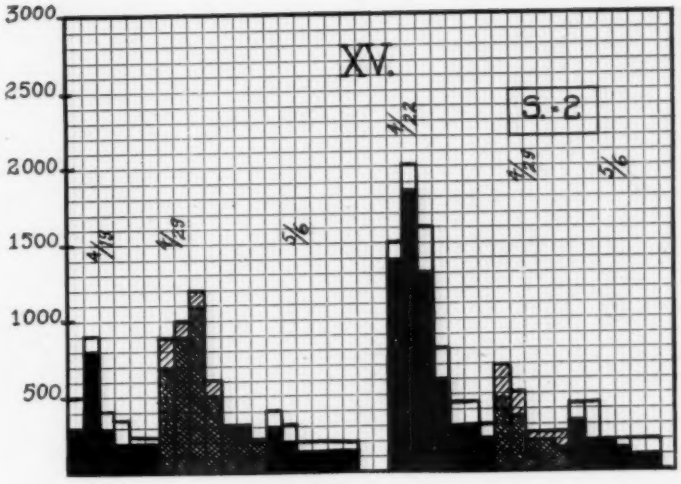

CHART 5

BOOK REVIEW

The Principles and Practice of Medicine. Designed for the use of Practitioners and Students of Medicine. Originally written by the late SIR WILLIAM OSLER, Bart., M.D., F.R.S. Twelfth Edition: Revision by Thomas McCrae, M.D. pp. 1196. $8.50. (*D. Appleton-Century Company Inc., New York and London, 1935.*)

In the preface to the eighth edition of his textbook of medicine, the last edition with which Sir William Osler had any part in its preparation, he wrote: "Comparing the first edition with the present, very little remains of the original work," and alludes to the "extraordinary growth of our knowledge particularly in the department of the infectious diseases." With the eighth edition the publishers created a new page with new type.

There is a strange similarity in the attendant changes that have occurred with this the twelfth edition; largely rewritten and entirely reset with a new type-face, it has appeared after the death of the junior author, as did the earlier edition in 1920, after the death of Sir William Osler in November 1919. Great as had been the advance in our knowledge between the first and eighth editions, there has been almost if not quite as great an advance in the last sixteen years as in the previous twenty-five.

Among the single volume texts of medicine this one of Osler's, embodying the mature experience of a great clinician and clinical teacher, was recognized at once, upon its first appearance in 1892, as a masterly presentation of the subject and was accorded first rank, not alone among the English speaking peoples, but within a few years was translated into many foreign tongues including the Chinese.

The earlier editions appeared at a time in the evolution of our knowledge, when the fundamental structure leading to clinical medicine was based chiefly upon a broad and sound pathological experience. It was the age, in this country at least, of the early dominant influence of pathology and later of bacteriology upon the clinic. Osler's experience had been such as to qualify him in a unique way to profit by his wide pathological knowledge and to incorporate, with just the proper emphasis, those pathological changes significant and important for any proper appreciation of the clinical problem discussed.

And what shall one say of the value of such a text representing the lifelong experience of the writer, the sum of all the years of intimate contact with disease at the bed-side, as a teacher, and in the consulting room, when contrasted with so many modern texts having almost as many contributors as subject headings? The writer of this brief note still holds to the belief that, though there may be much to be gleaned from every seriously ordered text, there is an immeasurably added value in the authoritative writing of the single individual when, as in this

instance, the author was so eminent a teacher and clinician; and this quite apart from the contrast in style, English usage and charm which so distinguishes this from the modern texts.

When the time came that the responsibility of the future revision of Osler's Text-book of Medicine passed to another generation, no more fortunate choice could have been made than that of Dr. McCrae as Editor. He had been associated with Osler from the time of the appearance of the eighth edition and was abundantly qualified to carry on the work after Sir William's death in 1919, and now he too has gone.

We are keenly conscious of the great loss sustained by Medical Science in his untimely death. Dr. McCrae had carried through this last revision, constituting the twelfth edition of the Osler text, with a rare discrimination as to values, with an enthusiasm so characteristic of the man and with an unflagging devotion to the old traditions so much a part of his own life's work. Fortunately he had completed his task before the end came.

One has but to recall even superficially the enormous advances that have come about in Medicine during the last decade to appreciate the task of revision involved in this last edition. As McCrae says in the preface, "New diseases, or what seem new, appear; some grow less important; others disappear." The constantly increasing literature, much of it ephemeral, pours out in ever increasing floods and adds enormously to the task of separating the chaff from the grain. How extensively the text has been revised may be gathered from the list of sections, recorded in the preface, which have been materially altered or appear as new. The new type makes possible an increase in the number of words to the page, though slightly smaller than that used in the earlier editions, it is easily read and there are actually thirty-six fewer pages in this volume, which contains more material, than in the tenth edition.

The discussion on typhoid fever is in its familiar place, though occupying but thirty-three pages instead of forty-one as in the previous editions, and remains the best descriptive article of similar length in the language. It is interesting that typhoid fever has almost disappeared in many communities, and how difficult it is to teach today by bedside illustration. The same may be said of the section on malarial fever which is, as it always has been, an extremely interesting and succinct account incorporating both the historical and clinical data concerned, no unimportant part of which came from the Baltimore clinic. The section devoted to tuberculosis, always a matter of great interest and concern to Sir William, is admirably done. The discussion of the treatment is sufficiently detailed for a volume of this size. The pneumonias and pneumococcic infections are discussed in great detail, the text including reference to all the more recent important advances in our knowledge; bacteriology, infection and immunity and the morbid anatomy are sufficiently covered, the larger part of this section being given to the symptomatology, clinical course, complications and treatment in a clear, concise and extremely well written statement of all that is important. The paragraph upon the "crisis" is a wonderfully succinct description. The specific use of serum

might be given in more detail and some statement made as to the total amount that may be used in certain cases of severe infection. In discussing sudden death in certain instances in men who appear robust, the statement is made that "some of these cases are due to heart block" (p. 80). We wonder how often? We personally have never known an instance of proven death from heart block in pneumonia. We have encountered complete A-V dissociation from the too enthusiastic and wholly unnecessary use of digitalis in young adults and fibrillation rarely, but otherwise have not met with heart block in any aggravated form. We wish that Dr. McCrae had discussed in some detail the use, or the abuse, of digitalis in pneumonia.

Under the heading of the Specific Infectious Diseases, we note the inclusion under the sub-heading of Mycoses, of Nocardiosis, the Blastomycetes, Mycetoma, and Aspergillosis. Coccidioidol Granuloma is referred to under the Blastomycetes. Coccidiosis as a protozoan infection is described under Psorospermiasis. Is it possible that confusion might occur in this connection without a more definite statement as to the biological distinction?

The article on syphilis, as in the early editions, is an unusually satisfactory discussion. It contains several passages written with great human understanding and with the charm that so characterized all of Osler's writings. Would not some reference here to the more recent work that has appeared be a wise addition; especially so, since so much has come out of his old clinic?

One of the changes from the earlier editions is the dropping of Weil's disease from the index; neither is there any allusion to Weil's early observations in the description of spirochaetosis icterohaemorrhagica; (p. 275) though in the discussion of infectious jaundice (p. 352) the statement is made that "it is difficult to know where to classify the disease described by Weil in 1886." This is perhaps quite properly a step in the simplification of nomenclature, but in view of the long customary usage it is somewhat difficult to overlook.

The articles on variola, vaccinia, and vaccination are classical descriptions; the short historical paragraph on vaccination illustrates in an unusual way the rare gift with which Osler illuminated so many sections of his text. Were he living, how keenly would he have appreciated the story of the vaccination of the then Prince of Wales, later Edward VII, by direct inoculation from a successful take.[1]

Osler pays a just and an appreciative tribute, in the excellent account of yellow fever, to the significance of the yellow fever commission's observations, and to the heroic sacrifice of those men who were concerned in the attempt to solve the riddle of its etiology. One wishes, however, that there might have been a more detailed account of the work of Noguchi and his associates in the failure to prove his Leptospira icteroides as the causative agent. A brief discussion in this connection of the generally accepted belief in the identity of Leptospira icteroides and L. icterohemorrhagiae (Sellards and Theiler), of the failure to isolate Leptospira from West African yellow fever, and the confusion that may arise owing to

[1] Sir Austen Chamberlin, Down the Years, 1935.

the prevalence of infectious jaundice in South America, would be of value. It is highly probable that West African and South American yellow fever have the same causative agent, quite unknown but generally assumed to be a filterable virus.

The subject of rheumatic fever is considered somewhat in detail, and the description of the clinical course, and the various important and serious complications are all adequately reviewed. The paragraphs devoted to the involvement of the heart are sufficiently exhaustive. We are surprised at the statement of the incidence of electrocardiographic changes occurring in 90 per cent of the cases. This is greatly in excess of Parkinson's and Coomb's figures and also of our own series. With the statement (p. 340) that "the view is gaining ground that the manifestations of the disease represent a condition of hypersensitiveness to various forms of streptococci," we are not entirely sympathetic. One is somehow left with a sense of disappointment in the discussion of the rheumatic state. There is no allusion to Coburn's Monograph, to Coburn's and Pauli's Study on the relationship of Streptococcus hemolyticus to the rheumatic process, to Todd's paper on the conversion of certain hemolytic streptococci to non-hemolytic forms. In spite of the accumulated evidence supporting some sort of bacteriological sensitization as underlying or predisposing to, or even acting as, the etiological factor of the rheumatic state, the possibility of a filterable virus as the causative agent can not as yet be summarily dismissed. In its clinical description the text is admirable. The significance of a persistent leucocytosis and of the sedimentation rate might have been referred to. This section concludes with brief descriptions of infectious mononucleosis, epidemic stomatitis, psittacosis, epidemic diaphragmatic pleurodynia—allusion is made to the recent study in the Danish island of Barnholen but no reference is given—lymphogranuloma inguinale and a group of miscellaneous infections among which are phlebotomus fever, verruga peruviana and oroya fever. Are not the two latter accepted today as different stages of the same infectious process?

There follows an excellent section devoted to diseases due to physical agents with interesting but sufficiently detailed discussion of thermic fever, Caisson disease and gas poisoning. The increase in the incidence of carbon monoxide poisoning is a strange commentary upon the times. Under the heading of "intoxications," lead, mercury and food poisons are fully discussed. We note that Benzyl benzoate, endorsed in earlier editions, has been wisely omitted. In the discussion of the treatment of lead poisoning ammonium chloride is suggested, but there is no allusion to the intravenous use of calcium chloride as suggested by Aub and Minot. The value of sodium thiosulphate suggested in the treatment of both lead and mercury poisoning is, in our opinion, somewhat exaggerated. There is no allusion to the intravenous use of a 1 per cent solution of sodium formaldehyde sulphoxylate, as suggested by Rosenthal, in mercury poisoning in the early stage. The section devoted to food poisoning is excellent, including a discussion of ergotism, lathyrism and favism and a brief allusion to anaphylaxis.

Under the heading of deficiency diseases Pellagra, Beri-Beri, Scurvy and Rickets

are discussed in sufficient detail; the paragraph on the etiology of Pellagra though short is excellent, but is sodium thiosulphate of any use in its treatment? In this connection may we comment on the occasional similarity that may occur between endemic sprue and pellagra to which no allusion is made, and upon the very limited space given to sprue and its classification wholly upon a basis of symptomatology.

The section devoted to the diseases of metabolism has been altered to meet the modern advances in our knowledge. This applies especially to the discussion of diabetes. The paragraph discussing Insulin (p. 423) could profitably be rewritten, with a more positive statement as to the absolute necessity—not "if possible"—of blood sugar determinations, and attention to certain minor slips of English usage as "Some are best with the insulin" etc. Under chronic hyperinsulinism Von Gierke's disease finds a place for the first time.

Under the diseases of the digestive tract there are extremely valuable discussions of the congenital short oesophagus and the various acute and chronic lesions of the gullet. The diseases of the stomach including the neuroses and the disorders of the intestinal tract are discussed at length. There appears for the first time a brief statement of the digestive disturbances due to allergy.

The forty pages devoted to the diseases of the liver constitute, as in the former editions, one of the most important sections of the volume. The modern work of value has been referred to and is discussed with critical judgment. The amount of condensation of the facts known without sacrifice of the important points is quite remarkable. Van den Bergh's work is made use of and McNee's classification of jaundice is given, but we regret that there is no allusion to Rich's important work, or to his paper upon the pathogenesis of the forms of jaundice. The term acute necrosis of the liver appears as an alternative cation for acute yellow atrophy. Why not reverse the order?

Pancreatitis in its various forms and the disturbances of the peritoneum conclude the section on the digestive system. Under ascites we note that "the enlarged spleen in leukaemia, less commonly in malaria, may be associated with recurring ascites," of the 10th edition, becomes "an enlarged spleen may be" etc., in this edition.

Under the diseases of the respiratory system there are a number of minor changes in certain of the headings and in the description, all adding to the clearness and simplicity of the text. The dropping of the qualifying adjective "catarrhal" in connection with certain acute inflammations is significant. Bronchitis in all its various types is fully discussed, as are abscess, gangrene, collapse and new growths. Hay fever and Asthma are adequately treated. The description devoted to the circulatory disturbances of the lungs is, as it has always been, an admirable section. There are here a number of minor alterations in the text particularly in the discussion of pulmonary haemorrhage. Pleurisy, pneumothorax and the affections of the mediastinum are fully discussed.

Section eight is devoted to the diseases of the kidneys, malformations, movable kidney, nephritis, pyelitis, etc. The text is admirable and thoroughly in agreement with the present day teaching, though certain points might be profitably

discussed more in detail and other parts would bear additional pruning if necessary to gain space. Under paroxysmal hemoglobinuria there is no allusion to hemoglobin occurring as a threshold substance in the body.

The diseases of the blood-forming organs are adequately dealt with and the modern nomenclature is largely used. In discussing pernicious anemia the use of liver extract is of course discussed but not, perhaps, in a sufficiently detailed way, and the whole paragraph on treatment could be improved. Taken as a whole, however, the section is an extraordinarily concise and clear presentation of the subject.

The diseases of the circulatory system are covered in an unusually satisfactory section. Every possible disturbed function and pathological state is described in greater or less detail, as the circumstances demand. Cardiovascular heart disease and particularly the study of aneurism and arteriosclerosis had always a peculiar appeal to Osler. This section of the text has always impressed the writer as conspicuously successful. With the inclusion of figures to illustrate some of the arrhythmias we are not wholly sympathetic. We see no reason for inclusion of figures 5 and 6 (page 794). Figure 1 (page 787) appears upside down, but is probably of as much value as if it were right side up. Figure 2 has a partially inaccurate description. The clinical diagnosis of complete heart block would bear amplification. There is no reference to Peabody's work on the significance of the vital capacity. The clinical descriptions of acute and chronic valvular disease are excellent. But why allude to the fact that a successful valvulotomy has been accomplished in mitral stenosis? Once and once only!

The discussion of aortitis and of aneurism leaves little to be desired. It may, however, pertinently be asked how often does one encounter a so-called relative aortic insufficiency?

The diseases of the glands of internal secretion are perhaps sufficiently discussed. A fascinating subject in its many and far reaching possibilities, but it is a wise conservatism that limits any extended review. One wishes that the paragraph on adrenal therapy of Addison's disease had been slightly more detailed. It gives but an outline and could profitably be rewritten. In an otherwise excellent discussion of the thyroid gland, one or two statements need amplification. In discussing simple goiter, the sentence "The heart may be involved, possibly from pressure on the vagi. Other cardiac disturbances probably mean hyperthyroidism," is not a wholly satisfactory statement. The description of the myxoedematous state is extremely interesting both historically and clinically. The discussion of exophthalmic goitre is excellent, as is that on the disturbances due to the parathyroids, the pituitary and the so-called sex glands.

The chapter on the diseases of the nervous system concludes the volume. This section has always been the most satisfactory presentation of the subject in moderate compass that we know. In the earlier editions it bore the imprint of Dr. H. M. Thomas. All the really important advances in our knowledge of the subject have been incorporated and as elsewhere the text has been kept fully abreast of the present teaching.

We have commented above somewhat in detail for two reasons. We were anxious to note particularly how far the original text had been retained in all the fundamental and essentially important clinical descriptions, and secondly, how extensively the newer knowledge had been made use of. In both respects there is little to be desired. The text has all the rare gift of English usage that was so peculiarly Osler's art. It is true that as Dr. Osler wrote in 1920 there have been many changes in the text since the first edition. To some we have alluded. Anyone historically minded should read MacDermott's paper on the early editions (Annals Med. Hist., May, 1934).

The writer of this brief note has for many years regretted the fact that the bibliographical references of so many important papers, of importance both historically and clinically, appearing in the text were not given. It would, we believe, add immensely to the value of the volume if a bibliography could be included.

What we may ask is to be the future of this volume; a text that should be read by every student of medicine for its clinical description of disease if for nothing else. There are those who have expressed the opinion that it should be allowed to stand as it is without further attempts of revision. The writer does not share this view. We hope that there may be many subsequent editions of Osler's text under appropriate guidance; that the clinical descriptions may be left unaltered and that at least the important bibliography may be given. Even as it appears in this newest guise we know no single volume text that approaches it in the matter of sound conservative statement, charm of clinical description or historical allusion.

E. P. C.

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